Human reproductive cloning

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Introduction

This chapter aims at summarizing salient issues in human reproductive cloning (HRC), defined as "*The use of technologies, including somatic cell nuclear transfer* (SCNT)*, to create offspring with the shared genomic material of the original person*" [1]. In the course of this exposé, mention will also be made of human therapeutic cloning (HTC), defined as a method that "*uses these same experimental techniques for therapies other than reproduction* (*such as research, production of embryonic stem cell lines, or creation of solid organs for transplant*)" [1].

In order to position reproductive cloning within the realm of biology, it is opportune to stress that in the animal kingdom, reproductive processes are so diversified to include any conceivable mechanism: reproduction can be bisexual with internal (e.g., mammals) or external (e.g., invertebrates, amphibians, fish) copulation; in addition, there is the so-called *sequential hermaphroditism*, when in a species sex can be interchangeable (e.g., bearded dragons, red frogs, clownfish), *true hermaphroditism* (e.g., worms, moss animals, snails), and even *parthenogenesis* (e.g., some lizards and crustaceans).

This means that, at least in principle, reproduction by cloning may be considered as one of the many natural options. However, in evolutionary terms, each and every species developed over millennia its particular form of reproduction to better suit its needs. For mammals in general and the genus *Homo* in particular, evolution produced the arguably only mechanism capable of increasing diversity and improving

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the species. This is why it can be affirmed that, over and above the ethical reasons that will be discussed in detail, among humans, reproduction by cloning is directly against the evolutionary pathway set millions of years ago.

It can be argued that, with the advent of assisted reproduction technology (ART), a number of mammals, as well as humans, moved away from the evolutionary path set for our species. This, however, is only partially true, since the scope of ART is bisexual reproduction, albeit achieved through external fertilization and without copulation.

It has been said that, having accepted external fertilization, the next step, reproductive cloning when there are no sperm or eggs, may become acceptable, especially when a couple is opposed to sperm, or oocyte, donation or adoption.

More recently, work has been carried out on a technique, *in vitro gametogenesis* (IVG), that could possibly rectify germ cell aplasia (e.g., non-obstructive azoospermia and oocyte maturation failure syndrome). Today, primordial germ cells can be derived from pluripotent stem cells, although further progression to post-meiotic germ cells usually requires a gonadal niche and signals from gonadal somatic cells [2]. It has been argued that, "*if safety is the main reason for not allowing reproductive cloning, one might expect a similar conclusion for the reproductive application of IVG, since both technologies hold considerable and comparable risks*" [3]. This may be true, but, as the authors concede, risk is not the sole or even the main reason why cloning is being condemned. In fact, proponents of HRC call it *reproductive regeneration*, a term that, ironically, perfectly describes why there is such a widespread rejection of the technique: the fact that it negates the very essence of reproduction, *generation*, not *re-generation*.

As mentioned by the Ethics Committee of the American Society for Reproductive Medicine (ASRM), the prospect of using HRC has produced an intense debate involving "*lawmakers, academicians, ethicists, religious leaders, international and national agencies, professional societies, and others*" [1]. In the end, decisions will be based on two fundamental issues: on the one hand the safety and efficacy of the procedure and on the other laws or governmental regulations based on the intensity and extent of ethical objections.

Technical Aspects

The word "clon" was first used in the nineteenth century in botany, with the final 'e' added in 1903. It referred to the asexual propagation of any plant, mostly by replanting cuttings. The word was subsequently extended to natural/asexual, molecular, cellular, and artificial reproduction [4]. The word originates from the ancient Greek word κλών, meaning "twig," and is today utilized in biology to identify a group of identical entities and, more specifically, an organism that is a genetic copy of another organism. The term is utilized to identify the "copy" of an entire organism, as well as "copies" of molecules (such as DNA) and cells.

As mentioned, in nature cloning occurs in those species that produce their offspring without combining male and female genetic material. During the twentieth century, biologists have attempted to artificially clone first amphibians and, with

the advent of the twenty-first century, also mammals. The first mammalian born through cloning was the famous sheep Dolly in Scotland [5]. The absolute novelty consisted in the fact that her embryo was created using mature cells taken from an adult sheep mammary tissue. Although this achievement was hailed as a major revolution in reproduction, Dolly's premature illnesses led to the conclusion that she was afflicted by conditions typical of old age [6]. A genomic analysis of her DNA seemed to support the hypothesis of a premature aging due to telomere shortening [7]; however, in 2021, a concise, but accurate, summary of the situation [8] stressed that this finding contrasted with a number of investigations that generally found "*telomeres to* '*rejuvenate*' *during nuclear reprogramming*." In addition, several studies have now concluded that "*cloned offspring which survive beyond the neonatal period are healthy, age normally, produce viable offspring and animal products safe for human consumption*" [9].

Yet, enough concerns remain, and, as of 2022, a ban is enforced on commercial farm-animal cloning within the EU and the UK, but not the USA and a number of other countries.

With regard to human cloning, as we will see, these concerns have led to an outright ban on HRC at the international level.

The technique that allows cloning in mammals has been coined *somatic cell nuclear transfer* (SCNT). It consists of transferring the nucleus from a donor cell into an oocyte or an early embryo from which the chromosomes have been removed; depending on the species, there are many variations in the details of the method [10]. Initially, researchers envisaged to use SCNT as a way to determine whether genes remain functional even after most of them have been switched off when a specific type of cell starts to carry out a specialized function. In this respect, the fact that the DNA of a fully differentiated cell could revert to an undifferentiated status and become capable to initiate the process of embryonic development would demonstrate that all the genes in differentiated cells retain their functional capacity, although only a few remain active. Therefore, in terms of developmental biology, the greatest outcome of the new technique has been the discovery that yet-unknown factors in the recipient oocyte can reprogram the nucleus to a very early developmental stage. The technique has now been refined, with a major advance consisting in the use as the recipient cell of an oocyte enucleated at meiotic metaphase II [11]. Obviously, the critical step is the activation of the enucleated oocyte following insertion of the new nucleus. In this respect, during the physiological fertilization process, activation is induced by the release of intracellular calcium in a series of pulses that follow the sperm entry. Artificially, activation can be obtained through exposure to ethanol, strontium, or pulses of alternating current [10].

In 2003, two cloned rhesus monkeys were born [12], but success was obtained only following transfer of nuclei from 4- to 8-cell stage embryos and none following transfer at a later stage. This failure was attributed to removal during the process of enucleation of key factors from the oocyte.

Finally, in 2011, an experiment was carried out to exchange the genome of a human oocyte with that of a somatic cell; the experiment aimed at producing pluripotent stem cells to be used for cell replacement in subjects with degenerative human diseases. In the original experiment, the development of human oocytes after

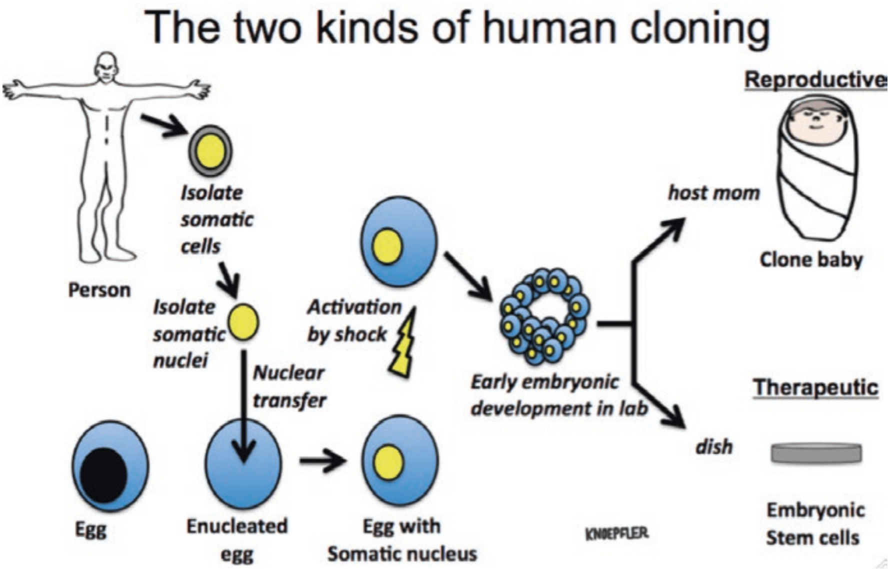

Fig. 8.1 Schematic representation of the two variant forms of human cloning: the first (***Reproductive cloning***) aimed at obtaining an individual with the same genetic and physical characteristics of the donor; the second (***Therapeutic cloning***) aimed at producing totipotent embryonic cell for research and therapeutic purposes (Reproduced from "The Niche" 2013, with permission). Schematic representation of the two variant forms of human cloning: the first (***Reproductive cloning***) aimed at obtaining an individual with the same genetic and physical characteristics of the donor; the second (***Therapeutic cloning***) aimed at producing totipotent embryonic cell for research and therapeutic purposes (Reproduced from "The Niche" 2013, with permission)

genome exchange arrested at late cleavage stages in association with transcriptional abnormalities [13].

If the blastocyst resulting from SCNT is transferred into the uterus of a female host and pregnancy progresses to term, the resulting individual will be a *clone*, since it will carry the same nuclear genetic material as the donor (Fig. 8.1). The expression "nuclear genetic material" of the adult somatic cell indicates that the offspring would not be an exact copy, because of the presence in the oocyte cytoplasm of a set of mitochondria, representing a prominent source of energy metabolism, but also containing a specific type of mitochondrial DNA that will later populate the cells of the offspring [14].

In sexual reproduction, clones are created when a fertilized egg splits to produce identical (monozygous) twins with identical genomes.

Attempts to Achieve Human Cloning

John Burdon Sanderson Haldane, a British scientist who was one of the founders of Neo-Darwinism, was the first to have thought of the possibility of human cloning and believed that it would 1 day be utilized to create super-human, super-talented individuals. He wrote: "*Assuming that cloning is possible, I expect that most clones*

would be made from people aged at least fifty, except for athletes and dancers, who would be cloned younger. They would be made from people who were held to have excelled in a socially acceptable accomplishment. … Other clones would be the asexual progeny of people with very rare capacities, whose value was problematic, for example permanent dark adaptation, lack of the pain sense, and special capacities for visceral perception and control. Centenarians, if reasonably healthy, would generally be cloned, if this is possible; not that longevity is necessarily desirable, but that data on its desirability are needed" [15].

In fact, in spite of this prediction, today there is an almost ubiquitous opposition to cloning for reproductive purposes coming from both the scientific community and the public at large. Haldane may have been aware that his words would 1 day be rejected, since he concluded: "*I'm not a biologist or a botanist, so I apologize if any of the above is ill-informed or incorrect, and I would be happy to be corrected, or to learn more*."

Because of the strong opposition, over the last decade, the few who are determined to proceed along the path leading to the birth of a cloned baby have been working in an atmosphere of mystery and secrecy not conducive to true scientific advances.

Since the turn of the millennium, there have been suggestions that HRC may represent a way to improve the human genetic endowment of mankind by cloning individuals of great achievements. Although these suggestions have generally never been taken seriously, some physicians have on occasion made clear that they were ready to carry out cloning [16], giving rise to a number of sensational reports on such attempts.

On 11 April 2002, Alison Abbott, in a short note in *Nature* [17], reported that European scientists had voiced skepticism about claims by the Italian gynecologist Severino Antinori that one of his patients was 2-month pregnant with a cloned human embryo. Ian Wilmut, senior member of the team that cloned Dolly the sheep, labeled the claim as "*either a misunderstanding, or deliberately misleading*." The following month, Antinori told the Italian magazine *Oggi* that three clones already existed: two boys and a girl who at the time were 9 years old and living in Eastern Europe. But, as usual, he provided no proof to confirm any of his claims! Then on 23 June 2002, the *Chicago Tribune* published that an "*informal consortium*," led by Antinori and the American andrologist Panayiotis Zavos, "*has currently 39 women in treatment*" to have a cloned baby and that 5 of these women were actually pregnant.

During December of 2002, the Geneva-based Raelian cult, which believes that humans were originally created by aliens, claimed that a baby girl named Eve had been born from an egg fertilized using a skin cell from her mother [18]. Allegedly, the cloning was carried out by a research outfit separate from the sect named *Clonaid*, and a few days later it was announced that a second clone, a girl, had been created and was born from a Dutch lesbian woman. However, Eve did not undergo genetic testing to compare her DNA to that of her mother's, the only way to prove or disprove the claim. As expected, no confirmation of these claims was ever published, and no DNA testing of the alleged second infant was ever carried out.

Unfortunately, the *tam-tam* of fake news continued, and, in a comment dated 22 April 2009, Andy Coghlan [19] stigmatized the "clone-mania," mentioning the claim by Zavos to have produced 14 cloned human embryos and transferred 11 of

them into the wombs of women. He explained that, while none of the embryos survived this time, "*the cloned child is coming*," since "*there is absolutely no way that it will not happen*."

Once again, there is a lack of scientific information supporting these claims, and a search of *PubMed* in January 2022 found no publication whatsoever by "Zavos and Antinori." When searching for "Antinori S.", 282 results were obtained; 15 were by Severino Antinori (starting in 1991), all totally unrelated to human cloning. All others were from three homonymous researchers. As for "Zavos P. M.," a total of 92 results were obtained. Two articled dealt with HRC: in the first [20], he claimed to "*have never stated that we intended to create the first cloned embryo and the first human being for reproductive purposes by ignoring the public's concerns and the scientific critics. We also never intended to ignore the contradictory results that scientists in the field of animal cloning have obtained during the past years*." Zavos went on describing how his team "*created the first human cloned embryo*," as "*the end result of using nine microsurgically enucleated human donor oocytes and fusing them via electrical stimulation and activation with whole human granulosa cells from a patient desiring to have a child via SCNT*." He went on mentioning that "*the resulting cloned embryo was allowed to develop further in culture for 4 days post-SCNT and reached the 8–10-cell stage*." He concluded: "*its development was observed and recorded, and the embryo was cryopreserved for future molecular analysis and other observations*" (see Fig. 8.2). Not surprisingly, his promise: "*Full*

Prentice DA

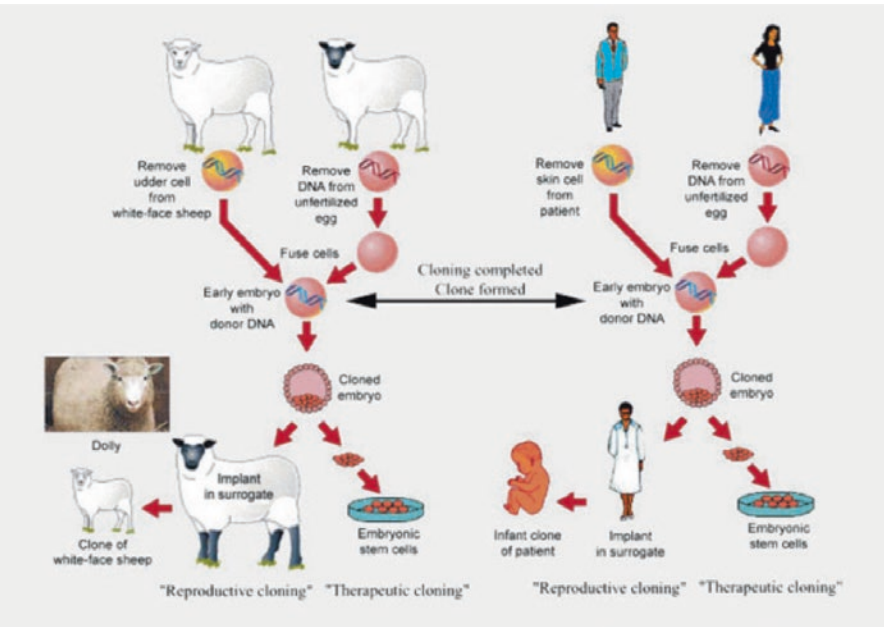

Fig. 8.2 Schematic representation of the procedure employed to clone the sheep Dolly (left portion of the figure). The same procedure would be employed when cloning a human being (right portion of the figure). (From Prentice DA, with permission)

documentation of the data of all of the accomplished results depicted herein will be described in detail in peer-reviewed journals" never materialized. The second article [21] seems to deal with the same procedure of the first, since it describes the preimplantation embryonic potential of fibroblasts from adult skin cells from an infertile man. The fibroblasts were fused with both enucleated bovine oocytes and human oocytes obtained from the wife. Oocytes reconstructed via somatic cell nuclear transfer were cultured *in vitro*. Of three reconstructed human oocytes, one developed to the four-cell stage and was subsequently transferred into the patient's uterus, but no pregnancy developed. Authors claimed this to be "*the first evidence of the creation and transfer of a human cloned embryo for reproductive purposes*."

In commenting Zavos results, Robert Edwards [22] cautioned: "*A wide perspective must be maintained on this work. Results in many animal species remain disastrous, as in mice, with many fetuses and offspring grossly malformed. Dolly has just died, seemingly prematurely*. *Results in cattle have greatly improved, with many embryos growing to full term. … Why do such immense differences arise between species*?". In a further comment, Azim Surani [23] stated that he was not convinced at all that the brief summary "*contains enough information to reach any valid conclusions*. … *The present paper is broad-brush treatment of a difficult subject that lacks attention to detail, and as such creates a false impression of the state of knowledge and efficiency of the procedure*." Surani in vain hoped that essential details would be forthcoming.

As mentioned, also in the case of HTC—i.e., the technique envisioned in order to generate matched nuclear transfer (NT)-ESCs by SCNT—initial reports did not stand up to scrutiny: In 2004 and 2005, two reports in the journal *Science* from a group led by the Korean researcher Hwang Woo-suk claimed to have obtained human ESCs by cloning [24, 25], but these experiments were shown to be fraudulent. In 2013 Tachibana et al. [26] identified a premature exit from meiosis in human oocytes coupled by a suboptimal activation as key factors responsible for failure of early attempts. By optimizing SCNT, they were able to circumvent these limitations, leading to successful derivation of human NT-ESCs displaying normal diploid karyotypes. These embryonic structures inherited their nuclear genome exclusively from parental somatic cells, and their gene expression and differentiation were similar to embryo-derived ESCs, suggesting an efficient reprogramming of somatic cells to a pluripotent state.

The following year, two teams generated embryonic stem cell lines by SCNT from adult human cells [27, 28], but there is at present a halt in work with this technique.

The Position of National and International Bodies Toward Human Reproductive Cloning

Over the years that followed the first claims of having achieved HRC, opposition to it grew, not only within the public at large but also from almost every existing institution, national and international. Requests for banning research in this field have been made in a number of countries, and as of 2021, some 45 countries have

formally banned human cloning. Although no such prohibition exists at federal level in the USA, several individual states had done so.

At the international level, the World Health Organization (WHO) has been at the forefront of the campaign against HRC: as early as 1997, with a solemn and unanimous declaration, the World Health Assembly condemned any form of human cloning, affirming that "*the use of cloning for the replication of human beings is ethically unacceptable and contrary to human integrity and morality*" [29]. Intriguingly, the only member state opposing the declaration did so on the ground that it was not "strong enough." Opposition to HRC was reiterated by the WHO's Executive Board in 2005 [30].

Additional international documents followed the WHO's condemnation. Among them are as follows: the Universal Declaration on the Human Genome and Human Rights, adopted by the UNESCO (United Nations Educational, Scientific and Cultural Organization) General Conference in 1997 and endorsed by the United Nations General Assembly the following year, and the World Medical Association's Resolution on Cloning, approved in 1997.

Elaboration of an international convention against HRC has been under consideration in the United Nations since December 2001. Although all countries oppose the procedure, some favored a comprehensive ban to include also HTC; others wanted the ban to cover only HRC. Often, when members of intergovernmental organizations cannot agree on a form of binding international law, they can settle for a declaration, which is less demanding. This is what happened at the UN: After 4 years of debate, on March 2005 the UN General Assembly approved a Resolution calling on member states to "*adopt all measures necessary to prohibit all forms of human cloning, inasmuch as they are incompatible with human dignity and the protection of human life*." The text was adopted by a vote of 84 in favor to 34 against, with 37 abstentions. The resolution also contained a call "*to protect adequately human life in the application of life sciences; to prohibit the application of genetic engineering techniques that may be contrary to human dignity; to prevent the exploitation of women in the application of life sciences; and to adopt and implement national legislation in that connection*" [31].

In 2008, UNESCO decided to add its voice to that of WHO and the UN, and its Bioethics Program began to investigate the possibility of a convention on cloning. There was tension between the independent experts supporting a ban on HRC, and member states concerned that disagreement would again surface, and ultimately the idea of a cloning convention dropped from UNESCO's agendas in 2012. The idea was taken up again in 2014, but despite a growing consensus, as of the end of 2021, there has been no move on the part of UNESCO to start to develop a treaty [32].

This situation is considered unsatisfactory because, for those states that have yet to formulate national regulations or policies on HRC, the absence of a clear international guidance may hinder an affirmative action.

The Inter Academy Partnership (IAP) is an umbrella organization comprising more than 140 national, regional, and global member academies, working together to support the role of science in seeking evidence-based solutions to global challenging problems. In 2013, IAP issued a statement calling for a ban on HRC while,

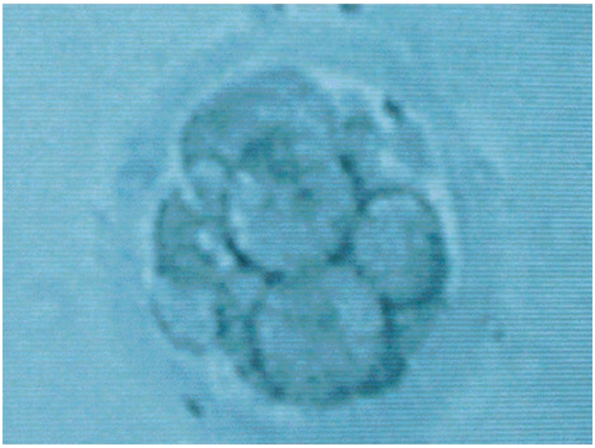

Fig. 8.3 An 8–10-cell human embryo derived from somatic cell nuclear transfer of granulosa, at 92 h. (From Zavos, 2003 [15])

at the same time, excluding from this ban cloning to obtain embryonic stem cells for both research and therapeutic purposes (see Fig. 8.3).

In conclusion, on the one hand, there has been widespread opposition to the cloning of a human individual on ethical grounds even before scientists started cautioning that there are major technical problems to be resolved; on the other, the way to an international treaty is still full of obstacles.

Ethical Considerations

An early publication by Savulescu [33] produced a list of arguments against or in favor of human cloning, bearing in mind that he mixed HRC and HTC.

On the negative side he listed

1. It is liable to abuse.
2. It violates a person's right to individuality, autonomy, selfhood, etc.
3. It violates a person's right to genetic individuality (whatever that is—identical twins cannot have such a right).
4. It allows eugenic selection.
5. It uses people as a means.
6. Clones are worse-off in terms of well-being, especially physiological well-being.
7. There are safety concerns, especially an increased risk of serious genetic malformations, cancer, or shortened lifespan.

Arguments in favor of HRC include

1. General liberty justifications.
2. Freedom to make personal reproductive choices.
3. Freedom of scientific inquiry.

4. Achieving a sense of immortality.
5. Eugenic selection (with or without gene therapy/enhancement).
6. Social utility—cloning socially important people.
7. Treatment of infertility (with or without gene therapy/enhancement).
8. Replacement of a loved dead relative (with or without gene therapy/enhancement).
9. "Insurance"—freeze a split embryo in case something happens to the first: as a source of tissue or as replacement for the first.
10. Source of human cells or tissues.
11. Research into stem cell differentiation to provide an understanding of aging and oncogenesis.
12. Cloning to prevent a genetic disease.

In commenting Savulescu's list, Williamson [34] stressed the importance of the right of a person to individuality, autonomy, and identity, associated with the right of not becoming a "means."

A substantial argument is that proposed by Jonas [35] who pointed out that technology requires developing an expanded conception of responsibility. Indeed, those with access to modern technologies raise the prospect of modifying our own genetic nature and significantly affect future generations. In this context, a cloned individual would be the victim of a clear violation of the basic right not to receive unrequested information about one's genetic status: A cloned young adult will inevitably know to have all genetic abnormalities he/she will see in the person with whom he/she shared the entire genome.

In order to evaluate the abovementioned arguments in a simple, yet unbiased manner, an essay published in 2002 [36] proposed to utilize two very simple criteria to evaluate reproductive cloning [37]:

1. Any technique aimed at producing an offspring who is the biological child of the *two* members of the couple involved must be—in principle at least—considered legitimate. This does not mean that every technique not fulfilling this criterion must be automatically labeled as unethical or—even worse, banned. Indeed, in a modern, democratic, and pluralistic society, where a number of ethical viewpoints coexist, legislation should only outlaw those techniques that are perceived as *causing damage*.

   It is easy to recognize that this is a concept difficult to define. Indeed, a technique could produce physical damage to the individual submitting to it, or to the offspring; it could also impact negatively on the psychological status of the individual born thanks to the technique, and it could have negative consequences for a community, or society at large.
2. Reproduction (irrespective of whether it is achieved through natural means or following medical assistance) must be considered a project aimed at giving birth to a new human being with rights that are identical to those of her/his parents, not a process to produce a child "at all costs."

> Such a principle was recognized very early in the ample debate that took place in the United Kingdom, the first country to be confronted with assisted reproduction. The *Code of Practice* of the *Human Fertilisation and Embryology Authority*, issued in its revised form in 1993, states clearly that one of its aims is "a concern for the welfare of the children, which cannot always be adequately protected by concerns for the interests of the adults involved" [38].

For those accepting these principles, as the international community seems to have done, HRC cannot be considered an important aid to people with no gametes who wish to reproduce, because—as mentioned—the technique contradicts the very basis of reproduction. First of all, reproductive cloning will not help couples wishing to have their own biological children, since in this case the offspring will only be the biological child of one parent, especially when a woman has no ovaries and therefore not even the maternally inherited cytoplasmic DNA can be passed to the child.

Finally, HRC allows the dominance of one human being (the nucleus donor) on the corporeal identity of another human being (the cloned one), representing a clear attempt at selecting the physical characteristics of a person, a fact contrary to the basic ethical principle of equality, since the clone will not have the opportunity to enjoy the diversity resulting from randomly inheriting its DNA from a man and a woman.

Based on these overarching principles, a number of bodies concerned with ethics have condemned HRC. In July 2002, the PCB, President's Council of Bioethics (established by the President of the USA), has forcefully addressed the issue of HRC affirming that proponents have defended their position "*by appeals to the good of freedom, existence* (*as opposed to non-existence*) *and well-being*." To this the PCB has responded that these arguments "*overemphasize the freedom, desires and control of parents and pay insufficient attention to the well-being of the cloned child-to-be*." They concluded: "*The Council holds that, once the child-to-be is carefully considered, these arguments are not sufficient to overcome the powerful case against engaging in cloning-to-produce-children*." The PCB unanimously reached the uniquely strong conclusion that rejection—on moral grounds—of cloning for human reproduction "*is not, as sometimes implied, a merely temporary objection, easily removed by the improvement of technique*." In fact, there are "*reasons for believing that the safety risks might be enduring*" and "*that conducting experiments in an effort to make cloning-to-produce children safer would itself be an unacceptable violation of norms of research ethics*." For this reason, "*there seems to be no ethical way to try to discover whether cloning-to-produce-children can become safe, now or in the future*" [39].

The ASRM issued a document in 2016 [1], stressing that "*reproductive SCNT* (somatic cell nuclear transfer) *has been inefficient in non-human species, with relatively few births reported in veterinary studies. It also has been associated with harmful complications in most mammalian species, including high fetal and neonatal death rates and/or imprinting and developmental disorders*." The document

accepts the fact that technological progress can increasingly reduce complications, but—as stated by Robert Edwards [22]—"*Cloning is still a matter of argument about animals, where results in most, if not all, species so far cloned by nuclear transfer have been appalling. Perhaps no-one would accept moving to human studies while disasters, evidently due to imprinting, afflict virtually every cloned offspring*." The ASRM document summarizes arguments against and in favor of HRC [1]: Opponents voice the fact that both natural conceptions, or one of the forms of assisted reproduction, involve the birth of an offspring with a uniquely mixed genetic lineage, whereas, following HRC, the offspring will have the genome of the donor of the somatic cell utilized. For this reason, no situation can justify recurring to it. On the opposite front: "*In the case of infertile couples in which one or neither partner can produce gametes, two situations might apply. If the male partner cannot reproduce with his spermatozoa, reproductive SCNT with his somatic cell would enable him to have a genetic tie with the child. His partner would have a biological tie if she donates the recipient oocyte or gestates the child. If the female partner cannot reproduce with her ova, transferring the nuclear DNA from her somatic cell to an enucleated donor oocyte would allow her to have a genetic relation to the child, although her partner would not*."

In conclusion, the committee believes that "*As long as the safety of reproductive SCNT is uncertain and infertile individuals/couples have alternatives for conception, the application of reproductive SCNT by medical professionals does not meet standards of ethical acceptability*." The document, however, leaves unanswered the main question posed by the PCB that it would be impossible to arrive in an ethical way at a safe way to use HRC.

Of interest is the statement that a negative outlook at HRC "*should not, however, be used to prohibit research in therapeutic SCNT, which can be ethically justifiable*."

Conclusions

Two types of concerns have surfaced in the debate over human cloning: *safety* and *human rights*.

On the safety issue, it has been argued that widespread hostility is inherent in an illogical and, therefore, transient fear of every new technology. Indeed, it has been documented that human low fecundability is due to a fairly large rate of re-absorption of early, severely malformed embryo indicating the existence of mechanisms capable of recognizing and eliminating the vast majority of developmental errors [40]. In addition, proponents argue that with presently available diagnostic tools, even if errors occur, they can be easily identified and dealt with. This approach must be held unethical since it considers a new human being a "commodity," to be created and eliminated if defective.

On the ethical front, whereas it is true that, as scientific knowledge proceeds, ethical considerations may also evolve, the fact remains that—at present and for the foreseeable future—there seems to be no ethical way to investigate whether

cloning-to-produce-children can become safe. More fundamentally, HRC deprives the new individual of one of its basic human rights, that of being born out of the diversity inherent in sexual reproduction.

References

1. American Society for Reproductive Medicine (ASRM) Ethics Committee Report. Human somatic cell nuclear transfer. Fertil Steril. 2016;105:e1–4.
2. Hong TK, Song J-H, Lee S-B, Do J-T. Germ cell derivation from pluripotent stem cells for understanding in vitro gametogenesis. Cell. 2021;10:1889.
3. Segers S, Guido Pennings G, Dondorp W, de Wert G, Mertes H. In vitro gametogenesis and reproductive cloning: can we allow one while banning the other? Bioethics. 2019;33:68–75.
4. Zafarris J. The etymology of “clone”. https://uselessetymology.com/2018/05/16/the-etymology-of-clone/.
5. Campbell KH, McWhir J, Ritchie WA, Wilmut I. Sheep cloned by nuclear transfer from a cultured cell line. Nature. 1996;380(6569):64–6.
6. Rhind S, Cui W, King T, Ritchie W, Wylie D, Wilmut I. 69 Dolly: a final report. Reprod Fertil Dev. 2004;16:156.
7. Shiels PG, Kind AJ, Campbell KH, Waddington D, Wilmut I, Colman A, Schnieke AE. Analysis of telomere lengths in cloned sheep. Nature. 1999;399:316–7.
8. Sinclair KD. Dolly at 25… is she ‘… still goin’ strong? Reproduction. 2021;162:E1–3.
9. Sinclair KD, Corr SA, Gutierrez CG, Fisher PA, Lee JH, Rathbone AJ, Choi I, Campbell KH, Gardner DS. Healthy ageing of cloned sheep. Nat Commun. 2016;7:12359.
10. Wilmut I, Bai Y, Taylor J. Somatic cell nuclear transfer: origins, the present position and future opportunities. Philos Trans R Soc Lond Ser B Biol Sci. 2015;370(1680):20140366.
11. Tsunoda Y, Shioda Y, Onodera M, Nakamura K, Uchida T. Differential sensitivity of mouse pronuclei and zygote cytoplasm to Hoechst staining and ultraviolet irradiation. J Reprod Fertil. 1988;82:173–8.
12. Simerly C, Dominko T, Navara C, Payne C, Capuano S, Gosman G, Chong KY, Takahashi D, Chace C, Compton D, Hewitson L, Schatten G. Molecular correlates of primate nuclear transfer failures. Science. 2003;300(5617):297.
13. Noggle S, Fung H-L, Gore A, Martinez H, Crumm Satriani K, Prosser R, Oum K, Paull D, Druckenmiller S, Freeby M, Greenberg E, Zhang K, Goland R, Sauer MV, Leibel RL, Egli D. Human oocytes reprogram somatic cells to a pluripotent state. Nature. 2011;478(7367):70–5.
14. Kim K, Kenigsberg S, Jurisicova A, Bentov Y. The role of mitochondria in oocyte and early embryo health. OBM Genetics. 2019;3:29.
15. Haldane JBS. Biological possibilities for the human species of the next ten thousand years. In: Wolstenholme G, editor. Man and his future. Boston: Little, Brown and Co.; 1963.
16. Writer S. In the news: Antinori and Zavos. Times Higher Education. www.timeshighereducation.co.uk/164313.article. Accessed 10 Aug 2001.
17. Abbot A. Disbelief greets claim for creation of first human clone. Nature. 2002;416:570.
18. Cult scientists claim first human cloning. The Guardian. https://www.theguardian.com/science/2002/dec/28/genetics.science. Accessed 28 Dec 2002.
19. Coghlan A. Latest human cloning claims leave sour taste. https://www.newscientist.com/article/dn17002-latest-human-cloning-claims-leave-sour-taste/. Accessed 22 Apr 2009.
20. Zavos PM. Human reproductive cloning: the time is near. Reprod Biomed Online. 2003;6:397–8.
21. Zavos PM, Illmensee K. Possible therapy of male infertility by reproductive cloning: one cloned human 4-cell embryo. Arch Androl. 2006;52:243–54.
22. Edwards RG. Human reproductive cloning a step nearer. Reprod BioMed Online. 2003;6:399–400.
23. Surani A. False impressions on human cloning. Reprod Biomed Online. 2003;6:398–9.

24. Hwang WS, Ryu YJ, Park JH, Park ES, Lee EG, Koo JM, Jeon HY, Lee BC, Kang SK, Kim SJ, Ahn C, Hwang JH, Park KY, Cibelli JB, Moon SY. Evidence of a pluripotent human embryonic stem cell line derived from a cloned blastocyst. Science. 2004;303(5664):1669–74.
25. Hwang WS, Roh SI, Lee BC, Kang SK, Kwon DK, Kim S, Kim SJ, Park SW, Kwon HS, Lee CK, Lee JB, Kim JM, Ahn C, Paek SH, Chang SS, Koo JJ, Yoon HS, Hwang JH, Hwang YY, Park YS, Oh SK, Kim HS, Park JH, Moon SY, Schatten G. Patient-specific embryonic stem cells derived from human SCNT blastocysts. Science. 2005;308(5729):1777–83.
26. Tachibana M, Amato P, Sparman M, Marti Gutierrez N, Tippner-Hedges R, Ma H, Kang E, Fulati A, Lee H-S, Sritanaudomchai H, Masterson K, Larson J, Eaton D, Sadler-Fredd K, Battaglia D, Lee D, Wu D, Jensen J, Patton P, Gokhale S, Stouffer RL, Wolf D, Mitalipov S. Human embryonic stem cells derived by somatic cell nuclear transfer. Cell. 2013;153:1228–38.
27. Yamada M, Johannesson B, Sagi I, Cole Burnett L, Kort DH, Prosser RW, Paull D, Nestor MW, Freeby M, Greenberg E, Goland RS, Leibel RL, Solomon SL, Benvenisty N, Sauer MV, Egli D. Human oocytes reprogram adult somatic nuclei of a type 1 diabetic to diploid pluripotent stem cells. Nature. 2014;510:533–6.
28. Chung YG, Eum JH, Lee JE, Shim SH, Sepilian V, Hong SW, Lee Y, Treff NR, Choi YH, Kimbrel EA, Dittman RE, Lanza R, Lee DR. Human somatic cell nuclear transfer using adult cells. Cell Stem Cell. 2014;14:777–80.
29. World Health Organization. Cloning in human reproduction. Fiftieth world health assembly. Geneva: World Health Organization; 1997.
30. World Health Organization, Executive Board. Reproductive cloning of human beings: status of the debate in the United Nations General Assembly: report by the Secretariat. https://apps.who.int/iris/handle/10665/20263.
31. United Nations. General assembly adopts United Nations declaration on human cloning by vote of 84-34-37. New York: United Nations; 2005.
32. Langlois A. The global governance of human cloning: the case of UNESCO. Palgrave Commun. 2017;3:17019.
33. Savulescu J. Should we clone human beings? Cloning as a source of tissue for transplantation. J Med Ethics. 1999;25:87–95.
34. Williamson R. Human reproductive cloning is unethical because it undermines autonomy: commentary on Savulescu. J Med Ethics. 1999;25:96–7.
35. Jonas H. Technology and responsibility: reflections on the new tasks of ethics. In: Sandler RL, editor. Ethics and emerging technologies. London: Palgrave Macmillan; 2014. p. 37–47.
36. Benagiano G, Primiero FM. Human reproductive cloning. Int J Obstet Gynecol. 2002;79:265–8.
37. Benagiano G. Reproductive strategies for human survival. Proceedings international conference “Robert G. Edwards at 75”. Reprod Biomed Online. 2002;4(suppl. 1):72–6.
38. Human Fertilisation and Embryology Authority. The embryo and fertilisation authority of the United Kingdom: code of practice. London: The HFEA; 1993.
39. The President’s Council on Bioethics. Human cloning and human dignity: an ethical enquiry. Washington, DC: President’s Council on Bioethics; 2002.
40. Benagiano G, Farris M, Grudzinskas G. The fate of fertilised human oocytes. Reprod Biomed Online. 2010;21:732–41.